Exhibit B

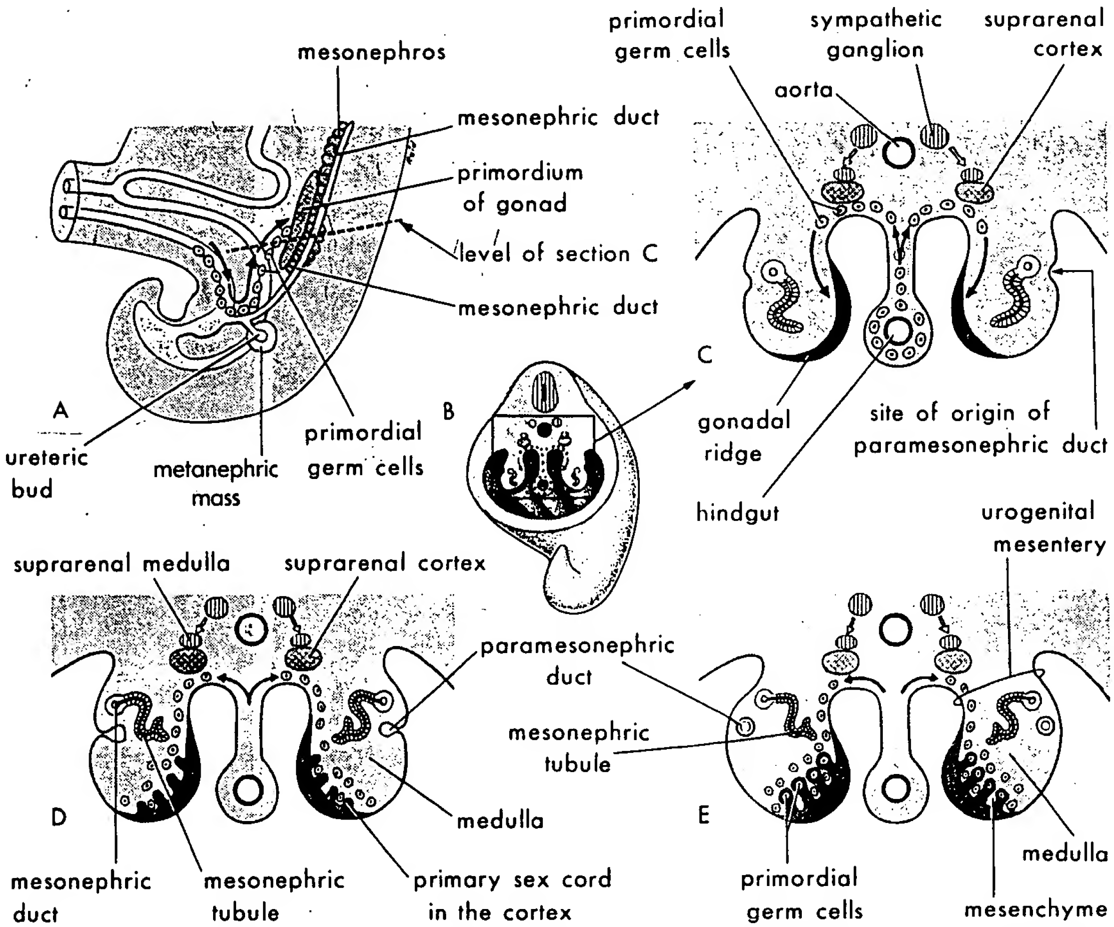

Figure 13–20. *A*, Sketch of a five-week embryo illustrating the migration of primordial germ cells from the yolk sac. *B*, Three-dimensional sketch of the caudal region of a five-week embryo, showing the location and extent of the gonadal ridges. *C*, Transverse section showing the primordium of the suprarenal (adrenal) glands, the gonadal ridges, and the migration of primordial germ cells into the developing gonads. *D*, Transverse section of a six-week embryo showing the primary sex cords and developing paramesonephric ducts. *E*, Similar section at later stage showing the indifferent gonads and mesonephric and paramesonephric ducts.

virilization of female fetuses. For details about the adrenal hyperplasias and their genetic basis, see New et al. (1989) and Thompson et al. (1991).

CAH is caused by a genetically determined deficiency of adrenal cortical enzymes necessary for the synthesis of various steroid hormones. The reduced hormone output results in an increased release of adrenocorticotropic hormone (ACTH), which causes adrenal hyperplasia and overproduction of androgens by the hyperplastic suprarenal glands.

THE GENITAL SYSTEM

Although the chromosomal and genetic sex of an embryo is determined at fertilization by the kind of sperm that fertilizes the ovum (p. 32), male and female morphological characteristics do not begin to develop until the seventh week. The early genital systems in the two sexes are similar; therefore, the initial period of early genital development is often referred to as the indifferent stage of sexual development.

Development of Gonads

The gonads (testes and ovaries) are derived from three sources (Fig. 13–20): the *mesothelium* (mesodermal epithelium) lining the posterior abdominal wall, the underlying *mesenchyme*, and the *primordial germ cells*.

The Indifferent or Undifferentiated Gonads (Figs. 13–20 and 13–21). The initial stages of gonadal development occur during the fifth week when a

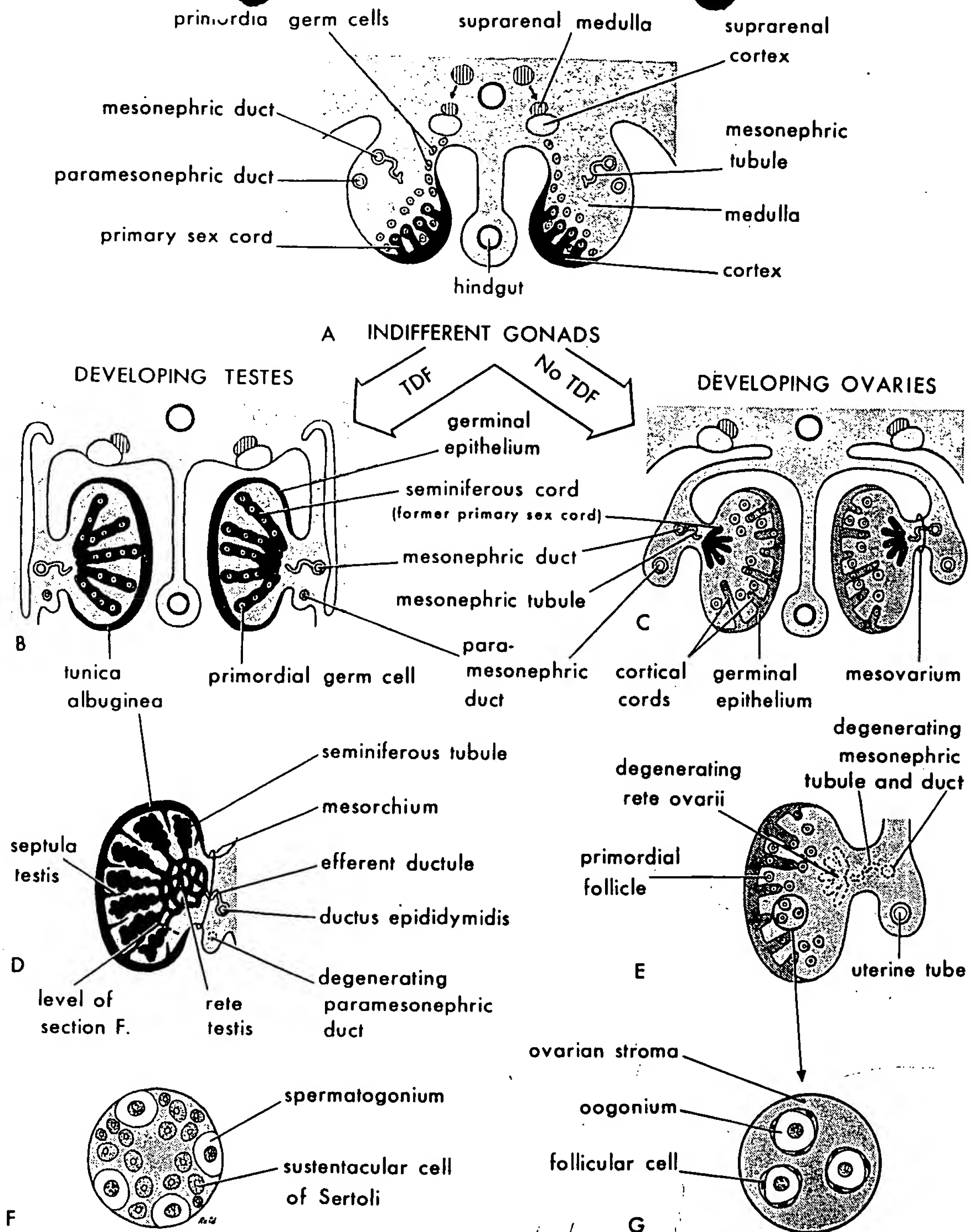

Figure 13–21. Schematic sections illustrating differentiation of the indifferent gonads into testes or ovaries. *A*, Six weeks, showing the indifferent or undifferentiated gonads composed of an outer cortex and an inner medulla. *B*, Seven weeks, showing testes developing under the influence of the testis-determining factor (TDF) on the Y chromosome. Note that the primary sex cords have become seminiferous cords. *C*, 12 weeks, showing ovaries beginning to develop in the absence of the TDF. Cortical cords have extended from the surface epithelium, displacing the primary sex cords centrally into the mesovarium where they form the rudimentary rete ovarii. *D*, Testis at 20 weeks, showing the rete testis and seminiferous tubules derived from the seminiferous cords. An efferent ductule has developed from a mesonephric tubule, and the mesonephric duct has become the duct of the epididymis. *E*, Ovary at 20 weeks, showing the primordial follicles formed from the cortical cords. *F*, Section of a seminiferous tubule from a 20-week fetus. Note that no lumen is present at this stage and that the seminiferous epithelium is composed of two kinds of cell. *G*, Section of the ovarian cortex of a 20-week fetus showing three primordial follicles containing oogonia.

thickened area of mesodermal epithelium develops on the medial side of the *mesonephros* (Figs. 13–4*F* and 13–20). Proliferation of this epithelium and of the underlying mesenchyme produces a bulge on the medial side of the mesonephros known as the *gonadal ridge* (Fig. 13–20*C*). Fingerlike epithelial cords called *primary sex cords* soon grow into the underlying mesenchyme (Fig. 13–20*D*). The "indifferent gonad" now consists of an external *cortex* and an internal *medulla.*

In embryos with an XX sex chromosome complex, the cortex of the indifferent gonad normally differentiates into an ovary and the medulla regresses. In embryos with an XY sex chromosome complex, the medulla normally differentiates into a testis, and the cortex regresses except for vestigial remnants (Table 13–1).

Primordial Germ Cells (Fig. 13–20). These large, spherical, primitive sex cells are visible early in the fourth week among the endodermal cells of the yolk sac near the origin of the allantois. During folding of the embryo (p. 70; see also Fig. 5–1), the dorsal part of the yolk sac is incorporated into the embryo. As this occurs, the primordial germ cells migrate along the dorsal mesentery of the hindgut to the gonadal ridges. During the sixth week the primordial germ cells enter the underlying mesenchyme and are incorporated in the *primary sex cords* (Fig. 13–20*E*).

Sex Determination. Chromosomal and genetic sex is established at fertilization and depends upon whether an X-bearing sperm or a Y-bearing sperm fertilizes the X-bearing ovum (p. 32). The type of gonads that develop is determined by the sex chromosome complex (XX or XY). Before the seventh week the gonads of the two sexes are identical in appearance and are referred to as "indifferent" or undifferentiated gonads (Fig. 13–21*A*). Development of the male phenotype requires a Y chromosome, but only the short arm of this chromosome is critical for sex determination. The gene for a *testis-determining factor* (TDF) has been localized in the "sex-determining region of the Y" (SRY) chromosome (Berta et al., 1990; Thompson et al., 1991). Two X chromosomes are required for the development of the female phenotype. A number of genes and regions of the X chromosome have special roles in sex determination.

The Y chromosome has a strong, testis-determining effect on the medulla of the indifferent gonad. It is the TDF (testis-determining factor) regulated by the Y chromosome that determines testicular differentiation. Under the influence of this organizing factor, the primary sex cords differentiate into seminiferous tubules (Fig. 13–21*B* and *D*). The absence of a Y chromosome (i.e., an XX sex chromosome complement) results in the formation of an ovary (Fig. 13–21*C* and *E*); thus, the type of sex chromosome complex established at fertilization determines the type of gonad that differentiates from the indifferent gonad (Mittwoch, 1992).

The type of gonads present then determines the type of sexual differentiation that occurs in the genital ducts and external genitalia (p. 290). It is the androgen testosterone, produced by the fetal testes, that determines maleness. Primary female sexual differentiation in the fetus does not depend on hormones; it occurs even if the ovaries are absent and apparently is not under hormonal influence.

In embryos with abnormal sex chromosome complexes (e.g., XXX or XXY), the number of X chromosomes appears to be unimportant in sex determination. If a *normal* Y chromosome is present, the embryo develops as a male. If no Y chromosome is present or the testis-determining region of the Y chromosome has been lost, female development occurs. The loss of an X chromosome does not appear to interfere with the migration of primordial germ cells to the gonadal ridges because some germ cells have been observed in the fetal gonads of 45,X females with Turner syndrome (Carr et al., 1968). Two X chromosomes are needed, however, to bring about complete ovarian development.

Development of Testes (Figs. 13–21*B*, *D*, and *F*, and 13–22*A* and *C*). Embryos with a Y chromosome in their sex chromosome complement usually develop testes. A coordinated sequence of genes leads to development of testes (Thompson et al., 1991). A gene on the short arm of the Y chromosome, designated as the *testis-determining factor* (TDF), acts as the switch that directs development of the indifferent or undifferentiated gonad into a testis (Berta et al., 1990; DiGeorge, 1992). TDF induces the primary sex cords to condense and extend into the medulla of the indifferent gonad where they branch and anastomose to form the *rete testis.* The connection of the prominent sex cords, now called *seminiferous (testicular) cords,* with the surface epithelium is disrupted when a thick, fibrous capsule called the tunica albuginea develops (Fig. 13–21*B* and *D*). The development of the dense *tunica albuginea* is the characteristic and diagnostic feature of testicular development. Gradually the enlarging testis separates from the degenerating mesonephros and becomes suspended by its own mesentery, the *mesorchium.* The seminiferous cords develop into the seminiferous tubules, tubuli recti, and rete testis (Fig. 13–21*D*).

The seminiferous tubules become separated by mesenchyme that gives rise to the *interstitial cells* (of Leydig). By about the eighth week, these cells begin to produce the male sex hormone *testosterone,* which induces masculine differentiation of the mesonephric ducts and the external genitalia. Testosterone production is stimulated by hCG (p. 40), which